European Journal of Internal Medicine 26 (2015) 646–651

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Clinical implications and outcome prediction in chronic hemodialysis patients with lower serum potassium × uric acid product

Ming-Yan Jiang [a], Jyh-Chang Hwang [a,b,*], Yi-Hua Lu [a], Charn-Ting Wang [a]

[a] Division of Nephrology, Chi Mei Medical Center, Tainan, Taiwan
[b] Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

ARTICLE INFO

Article history:
Received 20 May 2015
Received in revised form 19 June 2015
Accepted 28 June 2015
Available online 20 August 2015

Keywords:
Hypokalemia
Hyperuricemia
End-stage renal disease
Malnutrition
Inflammation
Chronic kidney disease

ABSTRACT

Background: The aims of this study were to evaluate correlations between serum potassium (S[K]) and uric acid (S[UA]) in hemodialysis patients and to determine whether lower levels of both S[K] and S[UA] were associated with poor long-term prognoses in these patients.
Methods: A cohort of 424 maintenance hemodialysis patients (58 ± 13 years of age; 47% male; 39% with diabetes) from a single center were divided into tertiles based on the product of S[K] × S[UA] (K × UA): Group 1: low K × UA: $n = 141$; Group 2: median K × UA: $n = 141$; and Group 3: high K × UA: $n = 142$. The longest observation period was 60 months.
Results: S[K] showed a positive linear correlation with S[UA] ($r = 0.33$; $p < 0.001$). In multivariate logistic regression analysis, Group 1 was characterized by hypoalbuminemia (odds ratio [OR] = 0.20, 95% confidence interval (CI) = 0.11–0.35) and lower levels of normalized protein catabolism [nPCR] (OR = 0.10, 95%CI = 0.05–0.22) and phosphate levels (OR = 0.41, 95%CI = 0.33–0.51). In contrast, Group 3 was associated with higher nPCR (OR = 6.07, 95%CI = 2.93–12.50) and albumin levels (OR = 2.12, 95% CI = 2.12–7.00). Compared to the reference (Group 1), the hazard ratio (HR) for long-term mortality was significantly lower in Groups 2 (HR = 0.65, 95%CI = 0.43–0.99) and 3 (HR = 0.56, 95%CI = 0.36–0.89). In multivariate Cox proportional analysis, the risk of mortality decreased by 2% (HR = 0.98; 95%CI = 0.96–0.99) per 1 unit increase in K × UA product.
Conclusion: Hemodialysis patients with lower S[K] and [UA] levels were characterized by hypoalbuminemia and lower nPCR, and they were associated with a long-term mortality risk.

1. Introduction

Hyperkalemia is a potentially life-threatening condition for patients with end-stage renal disease (ESRD) [1]. Furthermore, dialysate potassium concentration has been shown to have an impact on the outcomes of hyperkalemic hemodialysis (HD) patients [2]. Conversely, hypokalemia is usually overlooked as most patients are asymptomatic. Severe hypokalemia increases the risk of ventricular arrhythmias that can lead to cardiac arrest in patients with underlying cardiac diseases [3]. Chronic hypokalemic HD patients have also been shown to be associated with a worse long-term prognosis [4].

The prevalence of hyperuricemia and gout has been reported to increase with a decrease in glomerular filtration rate [5]. However, the association of serum uric acid concentration (S[UA]) and mortality in patients with ESRD is still controversial. A population-based study from the United States Renal Data System revealed that incidental gout was associated with a 1.5-fold increase in the risk of mortality in patients with ESRD [6]. In contrast, data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that a higher S[UA] was associated with a lower risk of all-cause and cardiovascular mortality in HD patients. A high S[UA] has also been reported to be related to a higher normalized protein catabolic rate (nPCR) [7].

In patients with ESRD, both potassium and UA homeostasis share a common pathway by depending on oral intake, dialytic removal, and adapted extra-renal excretion [8,9]. Their serum levels are elevated as renal function deteriorates. In addition, both serum potassium concentration (S[K]) [2,4] and S[UA] [7] levels have been positively associated with nPCR and plasma albumin level, which suggests the linkage of both parameters to protein nutritional status. However, few studies have investigated the association between S[K] and S[UA], although a high S[UA] (uric acid > 8.2 mg/dL) was found to be weakly associated with a lower S[K] in the DOPPS study [7].

Both S[UA] and S[K] are routinely monitored for chronic HD patients in clinical practice. Therefore, the aim of this study was to evaluate the

* Corresponding author at: 901 Zhonghua Rd., Yongkang Dist., Tainan City, Taiwan, 71010. Tel: +886 6 2812811, ext.: 57475; fax: +886 6 2816825.
E-mail address: alfonjch@seed.net.tw (J.-C. Hwang).

http://dx.doi.org/10.1016/j.ejim.2015.06.016
0953-6205/

correlation between S[K] and S[UA] in HD patients. We also combined these two biochemical markers to investigate whether lower levels of both S[K] and S[UA] were associated with a poor long-term prognosis in these patients, since both parameters are related to protein nutrition.

2. Patients and methods

2.1. Patient enrollment

This study was a cohort observational study of prospectively collected data based on a database that was constructed for outcome assurance from January 2004 to July 2008 at a single medical center. After excluding the patients who had received HD for fewer than 6 months (n = 18), those suspected of having acute renal failure (n = 6), and those with the long-term use of diuretics and potassium-reducing agents (n = 2), a total of 424 patients with ESRD undergoing maintenance HD at our unit three times a week for 4 hours per session in January 2004 were enrolled into this study. Based on the product of pre-dialysis (S[K] × S[UA]) as assessed on the last mid-week dialysis session in January 2004, the patients were categorized into tertiles: Group 1: S[K] × S[UA] ≤ 29.9, n = 141; Group 2: S[K] × S[UA] > 29.9 ≤ 38.3, n = 141; and Group 3: S[K] × S[UA] > 38.3, n = 142. The hollow-fiber dialyzers used in all patients included FB210G (Nissho Corporation, Osaka, Japan), B3-2.0 (Toray Industries Inc., Tokyo, Japan), Hemoflow F10 HPS (Fresenius Medical Care AG, Bad, Homburn, Germany), and PSN-210 (Baxter Healthcare Corporation, McGaw Park, IL, USA). The formula of the dialysate bath used at the initiation of the study was sodium 140.0 mmol/L, calcium 1.5 mmol/L, potassium 1.0 mmol/L, magnesium 0.5 mmol/L, chloride 104.5 mmol/L, acetate 4.0 mmol/L, dextrose 200 mg/dL, and bicarbonate 35 mmol/L (Renasol® SB-1080, Renal System, Minneapolis, MN, USA). Due to concerns over cost, we used another dialysate (Hemodialysis Concentrate A-35 and BP-11, Chi Sheng Chemical Corporation, Hsinchu, Taiwan) from July 2004 to the end of the study. The formula of this dialysate was sodium 139.0 mmol/L, calcium 1.5 mmol/L, potassium 2.0 mmol/L, magnesium 0.5 mmol/L, chloride 106.5 mmol/L, acetate 4.0 mmol/L, dextrose 200 mg/dL, and bicarbonate 39 mmol/L. No changes in potassium concentration in the dialysate bath or dialysate sodium remodeling process were applied throughout the study period. For management of anemia, 8000 units/week of Epoetinum alfa (EPREX®, Cilag AG, Switzerland) was subcutaneously injected after HD for patients with hemoglobin (Hg) less than 8.5 g/dL, 6000 units/week for those with Hg between 8.5 g/dL and 10 g/dL, 4000 units/week for Hg between 10 g/dL to 11 g/dL, and 2000 units/week for Hg between 11 and 12 g/dL. No patients received allopurinol and diuretics in this study.

2.2. Data collection

Blood samples were taken in the last mid-week of January 2004 (the beginning of the study), and every six months thereafter until September 2008. Pre-HD biochemical tests included serum albumin by means of bromocresol purple, and potassium, blood urea nitrogen, creatinine, uric acid, and phosphate concentrations were measured using a Hitachi 7601–110 Automatic Analyzer (Tokyo, Japan). Residual renal function (RRF) was calculated by MDRD formula. Hematocrit was measured using a Beckman Coulter LH755-A system (Fullerton, CA, USA). Levels of high sensitive C-reactive protein (hs-CRP) (CardioPhase® Siemens Healthcare Diagnostics Products, GmbH, Germany) and pre-albumin (immunochemically, Dade Behring Marburg GmbH, Germany) were also measured. The data of the patients who were transferred to other centers or who died during the study were omitted on a monthly basis. We also evaluated Kt/V urea (Gotch formula) and nPCR for all patients at the beginning of study to compare differences in dialysis dosage and protein intake between the groups [10].

2.3. Comorbidity

Comorbidities were assessed according to the past history recorded in the medical charts at the beginning of study. The diagnostic criteria for the various comorbid conditions were described in our previous study [11]. All patients' records/information were anonymized and de-identified prior to analysis. The current study was approved by the Ethics Committee of Chi Mei Medical Center and was conducted in accordance with the guiding principles for human experimentation of the Helsinki Declaration.

3. Statistical analysis

Appropriate χ^2 and ANOVA with post hoc Bonferroni tests were used for comparisons between categorical and continuous variables between

Table 1
Basic demographic characteristics of the three groups of patients.

	Group 1	Group 2	Group 3
	n = 141	n = 141	n = 142
Demographic factors			
Diabetes mellitus, %	50	39	27[b]
Male, %	35	51[a]	54[a]
Age at study, years	59 ± 14	58 ± 13	56 ± 12
HD vintage, months	50.4 ± 41.4	49.9 ± 43.9	43.2 ± 118.3
Ultrafiltration, L/session	2.5 ± 0.8	2.6 ± 0.8	2.9 ± 0.8
nPCR, g/kg/day	1.11 ± 0.31	1.27 ± 0.32[d,e]	1.37 ± 0.29[d]
Kt/V*	1.45 ± 0.25	1.43 ± 0.26	1.40 ± 0.25
Residual renal function, ml/min/1.73 m^2	6.57 ± 2.18	5.33 ± 1.65[d,e]	4.75 ± 1.30[d]
Mean pre-HD blood pressure, mm Hg	98 ± 19	94 ± 17	92 ± 20[c]
BMI, kg/m^2	21.6 ± 3.4	22.0 ± 3.4[e]	23.6 ± 3.8[d]
ACEI and/or ARB, %	26	28	26
Karnofsky score	71 ± 17	77 ± 17[c,e]	83 ± 16[d]
Clinical comorbidity, %			
Coronary artery disease	21	15	20
Congestive heart failure	4	2	4
Peripheral vascular disease	7	7	6
Stroke	14	14	6
Neoplasm	12	6	6
Chronic lung disease	1	1	1
Liver cirrhosis and/or hepatoma	4	5	1
Malnutrition	6	4	1
No comorbidity	46	57	65[b]
Mortality rate, %	37	29	23[a]
Laboratory data			
hs-CRP, mg/L, median	4.73	4.69	3.65
(1st–3rd quartile ranges)	(1.56–13.3)	(1.65–9.73)	(1.50–8.59)
Pre-albumin, mg/dL	27.7 ± 8.6	34.2 ± 9.1[d]	36.7 ± 9.1[d]
Albumin, g/dL	3.7 ± 0.5	4.0 ± 0.4[d]	4.1 ± 0.4[d]
Sodium, mmol/L	138.6 ± 3.0	138.7 ± 2.3	138.0 ± 2.4
Potassium, mmol/L	3.7 ± 0.6	4.5 ± 0.5[d,f]	5.2 ± 0.7[d]
Uric acid, mg/dL	6.4 ± 1.0	7.8 ± 0.9[d,f]	9.1 ± 1.5[d]
Potassium × uric acid	23.8 ± 4.8	34.5 ± 2.4[d,f]	47.7 ± 8.8[d]
Uric acid/potassium ratio	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
Phosphate, mg/dL	3.8 ± 1.2	4.9 ± 1.3[d,f]	5.6 ± 1.6[d]
BUN, mg/dL	57 ± 17	75 ± 16[d,f]	91 ± 20[d]
Creatinine, mg/dL	8.1 ± 2.1	10.0 ± 2.4[d,f]	11.1 ± 2.6[d]
Hemoglobin, g/dL	8.8 ± 1.6	9.2 ± 1.5	9.3 ± 1.5[c]

Abbreviations: HD: hemodialysis, nPCR: normalized protein catabolism rate, ACEI: angiotensinogen converting enzyme inhibitor, ARB: angiotensin receptor blockade, hs-CRP: high sensitivity C-reactive protein, BUN: blood urea nitrogen.
Statistics:
a: $p < 0.05$. b: $p < 0.001$ vs. group 1 (χ^2 tests).
c: $p < 0.05$, d: $p < 0.001$ vs. group 1 (ANOVA with post hoc Bonferroni tests).
e: $p < 0.05$, f: $p < 0.001$ vs. group 3 (ANOVA with post hoc Bonferroni tests).
* Gotch formula.